NON-INVASIVE DIAGNOSTIC METHOD FOR INTERSTITIAL CYSTITIS AND BLADDER CANCER

FIELD OF THE INVENTION

The invention is drawn to a non-invasive method for diagnosing or monitoring interstitial cystitis and bladder cancer in mammals, including humans.

BIBLIOGRAPHY

Complete bibliographic citations to the references cited below can be found in the "Bibliography," immediately preceding the claims. Each of the references cited below is incorporated herein by reference in its entirety.

DESCRIPTION OF THE PRIOR ART

Interstitial cystitis (IC) is a chronic inflammatory bladder condition characterized by urinary frequency and urgency, burning, and suprapubic pain. IC occurs predominately in women, many who suffer for years before a correct diagnosis is made. Sant, 1993. The etiology and pathogenesis of IC are unknown. Autoimmune and immune mechanisms have been implicated based on findings of immunoglobulin and complement deposits in affected bladders and of alterations in bladder mucin. Lynes et al., 1987. Defects in the protective mucosal layer of the bladder have also been suggested as a cause of IC. See, for instance, Parsons and Mulholland, 1987; Gillespie, 1993; and Parsons, 1993. A defect in the bladder surface glycosaminoglycan layer may allow toxic substances in the urine to enter the bladder wall and establish an inflammatory response. Matilla, 1983. However, defective bladder lining is not a uniform finding in IC patients. Nickel et al., 1993. Other proposed causes of interstitial cystitis include viral and bacterial infection, vascular or lymphatic obstruction, abnormal vasomotor control, genetic or endocrinologic deficiencies, and neurogenic or allergic causes. Messing, 1991.

IC is a syndrome characterized by chronic inflammation of the bladder wall resulting in tissue damage and reduced bladder capacity. The infiltrate of inflammatory cells into the bladder wall of IC sufferers is often composed predominantly of lymphocytes, with an increased number of plasma cells as the degree of inflammation increases. Lynes, 1990. Two clinical subtypes of IC are recognized: "Classic" IC is associated with perineural infiltrate, mucosal ulceration, and marked mast cell hyperplasia in the bladder wall. Ghoniem et al., 1993; Letourneau et al., 1992. "Nonulcerative" IC is associated with a relatively unaltered bladder mucosa and a sparse inflammatory response, although the same severe symptoms are present. Many reports have described a significant increase both in mast cell number and size in the bladder wall, particularly within the detrusor muscle in both classic and non-ulcerative IC. See, for instance, Sant and Meares, 1988; Feltis et al., 1987; Aldenborg et al., 1986; Christmas and Rode, 1991; Larsen et al., 1982; and Kastrup et al., 1983. Using electron microscopy, histopathological studies have demonstrated a marked increase in the number of mast cells in the bladder walls of IC patients, most of which are degranulated. Vliagoftis et al., 1992. Similarly, results of a small separate study have indicated that mast cells are also present in the bladder washings of classic IC patients. Lundeberg et al., 1993.

One study estimates that IC afflicts about 500,000 patients in the United States, with approximately 50,000 newly confirmed cases being identified annually. Hano, 1989.

Approximately 90% of IC patients are women. Ratner et al., 1992. Historically, IC has been extremely difficult to diagnose. The most frequently used diagnostic approach is by "exclusion." In effect, the IC diagnosis is made by ruling out urinary tract infections, tumors, and other bladder afflictions in patients suffering from the symptoms of suprapubic pain, frequency changes, incontinence, and increased urgency.

Current treatments for IC are not much more refined than current diagnostic methods. The presently accepted method utilizes bladder distention, which requires the administration of a general anesthesia and administration of dimethylsulfoxide or other therapeutics via bladder catheterization. The protocol is both painful and timeconsuming. Furthermore, because of the difficulty in obtaining a definitive diagnosis, significant occurrences of misdiagnosis make the conventional treatments more traumatic and less effective. It has been reported that misdiagnosis and inappropriate treatment actually aggravates the condition. *Medical World News,* 1986.

As noted above, the diagnosis of IC is made on the basis of exclusion of other bladder diseases. These means are supplemented by clinical observation and cystoscopic examination of the bladder. Despite numerous efforts at a definitive diagnostic method, IC lacks a universal objective assay for diagnosis or monitoring. Attempts have been made to employ immunohistochemical staining for Tamm-Horsfall protein (uromodulin) in bladder epithelium as a marker for IC. Stone et al., 1992. These studies showed no significant correlation between the presence of Tamm-Horsfall protein and IC. Because defects in the mucosal surface of the bladder have been implicated in IC, analysis of glycosaminoglycan uronate and macromolecular uronate concentrations also has been suggested as a possible diagnostic indicator of interstitial cystitis. However, the urine of IC patients do not consistently show low values of uronates. Hurst et al., 1993. In light of the high numbers of mast cells associated with IC, urine histamine levels have been analyzed to determine whether histamine might serve as an indicator of IC. Yun et al., 1992. Results of these studies revealed that there was no significant difference in urine histamine levels between the control group and the IC group. This indicates that a spot urine histamine test is not useful for diagnosis or monitoring of IC.

Bladder cancer is the fifth most common neoplasm and twelfth leading cause of cancer death in the United States. Males are affected three times more frequently than females. Numerous chemicals are suspected bladder cancer-forming agents. However, only cigarette smoking and occupational exposure to aromatic amines are well-established risk factors.

The most common clinical presentation of bladder cancer is hematuria. Frequently, however, the diagnosis of bladder cancer is delayed because the hematuria is either intermittent or attributed to other causes such as urinary tract infection or the use of anti-coagulants. Because hematuria is often intermittent, voided urine cytology of transitional cells is conventionally used to diagnose bladder cancer. If the urinary cytology is positive, then transitional cell cancer of the urothelium is almost certainly present. But, cytological examination of transitional cells may be negative in up to half of the patients with bladder cancer. Thus, negative cytological results do not rule out the presence of bladder cancer. See, for instance, Cohen and Johansson, 1992; and Badalament et al., 1987.

An added diagnostic complication is that because transitional cells line the urinary tract starting at the kidneys,